

Diagnosing and Managing Barrett's Esophagus

Based on a presentation by Richard E. Sampliner, MD

Presentation Summary

Although significant advances have been made in our understanding of Barrett's esophagus (BE), several questions remain. The answers will affect the way BE is defined, identified, monitored, and treated. This paper reviews the current definition of BE, the rationale for surveillance and risk stratification, the possible role of p53 mutations in adenocarcinoma, and the relationships among metaplasia, dysplasia, and adenocarcinoma.

The rising incidence of esophageal adenocarcinoma in Western cultures has prompted a reexamination of key and sometimes controversial Barrett's esophagus (BE) issues.¹ The definition of BE that has evolved over the past several years distinguishes between short- and long-segment BE. In general, BE is defined as a change from normal squamous epithelium to columnar epithelium in any part of the lining of the esophagus. If there are discrete tongues of any length above the squamocolumnar junction (SCJ), the presence of intestinal metaplasia must also be investigated, which requires biopsy.

Two recent studies support the connection between intestinal metaplasia at the Z-line and BE. In general, the more irregular the SCJ, the greater the likelihood of intestinal metaplasia. The frequency of intestinal metaplasia was as high as 88% in tongues more than 2 cm above the esophagogastric junction (EGJ); it

was 67% in tongues more than 3 cm above the EGJ.^{2,3}

Even if there is evidence of intestinal metaplasia in the gastric cardia, an irregular SCJ may not warrant a biopsy. The intestinal metaplasia must be found in the esophagus to justify a diagnosis of BE.

When and Where to Biopsy

The decision about whether to biopsy is straightforward. If the esophagus appears to be abnormal, a biopsy should be performed to determine whether the abnormality truly resides in the esophagus.

When to biopsy is another question. Although epidemiological evidence suggests that certain patient populations should be screened for BE, this remains controversial. Male patients 50 years or older with longstanding reflux symptoms are thought to be at a higher risk for developing adenocarcinoma of the esophagus, although the exact risk criteria have not been defined. A recent population-

based study associated the increased risk of esophageal adenocarcinoma with increased severity and duration of reflux symptoms (Table 1).⁴ Therefore, the rationale for BE screening stems from the increasing incidence of esophageal adenocarcinoma and the increased risk of esophageal adenocarcinoma with reflux symptoms. Intuitively, clinicians believe that early detection offers an improved opportunity for survival.

The Length of BE

Short-segment BE (ie, abnormal columnar mucosa less than 3 cm above the EGJ) was first described 12 years ago. In a study of 61 patients, 38% of the adenocarcinomas were found in patients with BE 1 to 3 cm long (as measured in the resected specimen, not at endoscopy). Thirty-three percent of the adenocarcinomas were found in patients with BE less than 1 cm long.⁵ A later study of 4 patients showed adenocarcinoma in BE 0.5 to 2 cm long, which reinforces the link between short-segment BE and adenocarcinoma.⁶

Long-segment BE is known to be associated with a higher risk of adenocarcinoma. Short-segment BE is more common, but its cancer risk is not as well defined. Long-segment BE demonstrates a higher frequency of dysplasia than short-segment BE; short-segment BE demonstrates a higher frequency of dysplasia than intestinal metaplasia of the gastric cardia.⁷⁻⁹ Dysplasia may, in fact, be considered a surrogate marker for adenocarcinoma. However, there is no evidence that the type of BE (short- or long-segment) dictates the speed of progression from metaplasia to dysplasia to adenocarcinoma in the individual patient. Surveillance intervals should therefore not depend upon the length of BE.

Documenting Short-Segment BE

Whether to document short-segment BE is still under discussion but,

in general, documentation is recommended. Data about Barrett's dysplasia and its progression to cancer are very limited. Seven prospective studies from 5 centers worldwide indicate that, in a limited dataset, only 2% of patients with no dysplasia develop cancer over a 3.6- to 10-year follow-up period. As expected, the percentage of patients who did get cancer increased with the severity grade of dysplasia (Table 2). Follow-up periods were variable, and so these data are of limited value, but they are the only data available upon which decisions can be based.¹⁰

Surveillance

The limited data suggest that if 2 endoscopies with biopsies show no dysplasia, future surveillance at 3-

Table 1. Reflux Symptoms and the Risk of Esophageal Adenocarcinoma

Variable		Adjusted Odds Ratio
Recurrent reflux	1/wk	7.7
Frequency	>3/wk	16.7
Severity symptom score	>4.5	20
Severity and duration	>20 years	43.5

Source: Adapted from reference 4.

Table 2. Severity of Barrett's Dysplasia: A Risk Factor for Cancer

Dysplasia	# Developed Cancer	Total in Study	Percent	Follow up (Year)
None	3	150	2	3.6-10
Low-grade	8	45	18	1.5-4.3
High-grade	38	127	30	0.2-9.5

Source: Adapted from reference 10.

year intervals may be considered safe. As clinical researchers gather more documentation on Barrett's dysplasia and cancer, the recommended interval may increase. For patients with confirmed low-grade dysplasia, yearly endoscopies and biopsies are adequate until the dysplasia disappears. It is important to survey these patients closely to ensure that low-grade dysplasia is not adjacent to or overlying a cancer.

With high-grade dysplasia, intervention is usually considered necessary, although this remains controversial. A recent survey of 455 gastroenterologists in the United States (79% were "community practitioners") showed that 96% perform endoscopic surveillance; 92% survey more often than every 3 years, even if

no dysplasia is present. For high-grade dysplasia, 82% of the clinicians surveyed recommend esophagectomy, and if dysplasia is present, 20% perform some form of endoscopic ablation therapy.¹¹ In practice, gastroenterologists take a conservative approach to surveillance.

The rationale for frequent surveillance comes from retrospective datasets (Table 3). The data clearly show that patients with known BE who are seen regularly have a much higher survival rate than those who are not.¹²⁻¹⁴

The decision about when to stop surveillance can be a difficult one because it forces the clinician to confront "politically incorrect" but very important issues. For example, when patients have no dysplasia and are 80 years of age, surveillance should be stopped, even if such patients are highly functional because it is likely that death from another cause will preempt esophageal adenocarcinoma. If patients are significantly functionally impaired, surveillance may be stopped even before the age of 80.

The concept of "near elimination" of esophageal acid in BE has been discussed frequently in recent literature. In a randomized trial of patients with BE taking either omeprazole 40 mg bid (a proton pump inhibitor) or ranitidine 150 mg bid (a histamine-2 receptor antagonist), the omeprazole-treated patients averaged only 1.4 minutes of pH less than 4 in a 24-hour period. After 2 years, the decrease in BE surface area was only 8%. This is statistically significant but not clinically significant. So, "near elimination" of acid is not a feasible approach to reversing BE.¹⁵

Risk Stratification

Clinicians use risk stratification to focus their efforts on those patients most likely to develop adenocarcinoma of the esophagus. The data show that sex, ethnicity, aneuploidy by flow cytometry, and age are impor-

Table 3. Endoscopic Surveillance and Outcome of Barrett's Esophagus

Study	Surveillance		No Surveillance	
	N	Survival (%)	N	Survival (%)
Streitz et al*	19	62 (5 year)	58	20 (5 year)
Peters et al†	17	90 (5 year)§	35	20 (5 year)
Van Sandick et al‡	16	86 (2 year)	54	43 (2 year)

Source: *Reference 12; †reference 13; ‡reference 14. §If the 4 patients with high-grade dysplasia only are excluded, P = 0.09.

Table 4. Presence of p53 Mutation in Barrett's Esophagus

Study	Dysplasia Grade (% with p53 mutation)			
	Negative	Low-Grade Dysplasia	High-Grade Dysplasia	Adenocarcinoma
Ramel et al*	5	15	45	53
Younes et al†	0	9	55	87

Source: *Reference 16; †reference 17.

tant risk factors. Older white males are the typical patients. Not surprisingly, the dysplasia grade is the most important factor; it remains the only validated marker for defining the risk of adenocarcinoma.

Studies of p53 mutations have shown promising results. The studies reveal an increasing presence of p53 mutations in patients with intestinal metaplasia, dysplasia, and adenocarcinoma of the esophagus (Table 4).^{16,17} In a recent study of patients with high-grade dysplasia but no cancer, 41% had a p53 mutation at each biopsy point in the metaplastic epithelium. Thus, this mutation could be a potentially powerful marker for cancer.¹⁸ Another recent study, in which serum antibodies to p53 appeared in patients before adenocarcinoma was diagnosed, suggests that p53 antibodies may also become a useful screening tool.¹⁹

Natural History of High-Grade Dysplasia

One unanswered question focuses on the cancer risk posed by high-grade dysplasia. The data available are limited and conflicting. The most recent sources suggest that cancer will develop in 15% to 31% of patients with high-grade dysplasia.^{20,21} Similarly, a study of 833 patients who underwent esophagoduodenoscopy showed that 62% had heartburn, 1.6% had long-segment BE, 6% had short-segment BE, and 5.6% had specialized intestinal metaplasia in the esophagogastric junction.⁸

Summary

Many questions about the proper diagnosis and management of BE remain, particularly in regard to the risk of esophageal adenocarcinoma. However, continued data collection will help to make clinical evaluations more straightforward in the future. Meanwhile, clinicians have several tools that can help them to identify the patients most at risk and to focus

surveillance on those who would most benefit from it.

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